

ORIGINAL ARTICLE

Cone beam computed tomography guided treatment delivery and planning verification for magnetic resonance imaging only radiotherapy of the brain

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ABSTRACT

Background. Radiotherapy based on MRI only (MRI-only RT) shows a promising potential for the brain. Much research focuses on creating a pseudo computed tomography (pCT) from MRI for treatment planning while little attention is often paid to the treatment delivery. Here, we investigate if cone beam CT (CBCT) can be used for MRI-only image-guided radiotherapy (IGRT) and for verifying the correctness of the corresponding pCT.

Material and methods. Six patients receiving palliative cranial RT were included in the study. Each patient had three-dimensional (3D) T1W MRI, a CBCT and a CT for reference. Further, a pCT was generated using a patch-based approach. MRI, pCT and CT were placed in the same frame of reference, matched to CBCT and the differences noted. Paired pCT-CT and pCT-CBCT data were created in bins of 10 HU and the absolute difference calculated. The data were converted to relative electron densities (RED) using the CT or a CBCT calibration curve. The latter was either based on a CBCT phantom (phan) or a paired CT-CBCT population (pop) of the five other patients.

Results. Non-significant (NS) differences in the pooled CT-CBCT, MRI-CBCT and pCT-CBCT transformations were noted. The largest deviations from the CT-CBCT reference were < 1 mm and 1° . The average median absolute error (MeAE) in HU was 184 ± 34 and 299 ± 34 on average for pCT-CT and pCT-CBCT, respectively, and was significantly different ($p < 0.01$) in each patient. The average MeAE in RED was 0.108 ± 0.025 , 0.104 ± 0.011 and 0.099 ± 0.017 for pCT-CT, pCT-CBCT phan ($p < 0.01$ on 2 patients) and pCT-CBCT pop (NS), respectively.

Conclusions. CBCT can be used for patient setup with either MRI or pCT as reference. The correctness of pCT can be verified from CBCT using a population-based calibration curve in the treatment geometry.

The use of magnetic resonance imaging (MRI) in radiotherapy (RT) shows a promising potential for treatment sites, such as the prostate and brain [1,2]. Registered MRI and computed tomography (CT) images are now commonly used in the delineation step of the RT chain but the registration introduces a systematic error of 2–5 mm for the brain [3,4]. RT based on MRI as the sole modality, so-called MRI-only RT, would remove the registration error and the associated potential hazards (under- and over-dosage of tumor and normal tissue, respectively). In MRI-only RT, electron densities need to be assigned to

MRI for accurate dose calculation and bone visualization [5]. Multiple approaches for creating CT-like images, a so-called pseudo CT (pCT) scan, from MRI scans of the brain have been suggested in the literature [6–8]. Although the scientific attention on MRI-guided treatment delivery is rapidly growing [9], little attention has been given to MRI-only based treatment delivery using traditional image guidance with x-rays [10,11]. Even though commercially available online MR-guided systems are emerging [9], the vast majority of RT courses will be carried out with x-ray based patient positioning in the foreseeable

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(Received 11 May 2015; accepted 10 June 2015)

future. In this study, we investigate if a kV cone beam CT (CBCT) obtained at the accelerator can be used for patient positioning in an MRI-only RT delivery situation. Further, we examine if CBCT can provide a reliable estimate of the error associated with the pCT created from MRI by comparing with the corresponding reference CT.

Material and methods

Six patients receiving cranial RT with palliative intent were included in the study. Each patient had a three-dimensional (3D) T1-weighted (T1W) MRI scan (Philips 1T Panorama HFO), a CBCT (Varian On-Board Imager v.1.6) and a CT (Philips Brilliance Big Bore CT) for reference. MRI scans were obtained with dual flex coils and scan parameters TE/TR = 6.9/25 ms, resolution = $0.85 \times 0.85 \times 1.2$ mm and FOV = $16 \times 16 \times 18$ cm. CBCT scan parameters were 100 kV and 74 mAs, resolution $0.5 \times 0.5 \times 2$ mm and FOV = $26 \times 26 \times 16$ cm. The CT scan was acquired with 120 kV and 400 mAs, resolution $0.64 \times 0.64 \times 2$ mm and FOV = $33 \times 33 \times 24$ cm. A pCT was generated for each patient using a patch-based approach described previously [8]. In brief, the approach aligns the patient's MRI scan with an atlas of co-registered MRI and CT scans. For each voxel in the patients MRI scan, a small sub-volume of voxels (a patch) around it is extracted and the locally most similar patches in the atlas are found. The corresponding average CT number in the atlas is then assigned to the voxel. As pCT is created directly from the MRI scan of the patient, it has the same resolution, frame of reference, body outline and field of view (FOV) as MRI. An example of the dataset of a patient can be seen in Supplementary Figure 1 (available online at: <http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1062546>).

Patient positioning

The CT was re-sliced to the resolution of MRI and cropped to the MRI body outline, placed in the same frame of reference and transferred to the registration workspace of Eclipse v. 10 (Varian Medical Systems). Here, the pCT, MRI and CT scans were auto-matched with CBCT using 6 degrees of freedom (DOF): anterior-posterior (AP), cranial-caudal (CC), right-left (RL), and, pitch, roll and jaw rotations. For the pCT and CT auto-matches, the match was performed on the bony anatomy (CT number > 200 HU). The auto-match SmartAdapt algorithm that was applied in the registration workspace works similar to the auto-match algorithm in the Varian Offline Review workspace used clinically [12]. All matches were considered to be of an acceptable clinical

quality, i.e. the bony anatomy of CBCT and reference was visually inspected to be on top of each other. The transformation matrix between the CT and CBCT was used as a reference and the difference as compared to pCT-CBCT and MRI-CBCT transformations was calculated. Paired pairwise t-tests were carried out for the MR and pCT differences of the pooled patient data for each DOF.

Calibration

Paired pCT-CBCT data were created by re-slicing CBCT to the pCT (MRI) resolution. Paired pCT-CT data in the same resolution were created for reference. To make fair comparisons, both pCT and CT were cropped to the body outline of CBCT. The CT numbers were transformed to relative electron densities (RED) using the treatment planning default calibration curve for the CT and pCT data [13]. For the CBCT RED transformation, a calibration curve based on either a CBCT phantom (Cirs Inc.) at 100 kV in a head simulated treatment geometry or a paired CT-CBCT population of the five other patients was applied (see Figure 1). For the latter, reference CT numbers and CBCT CT numbers were averaged in 100 HU bins for each patient. The known RED of the reference CT bins were then assigned to build

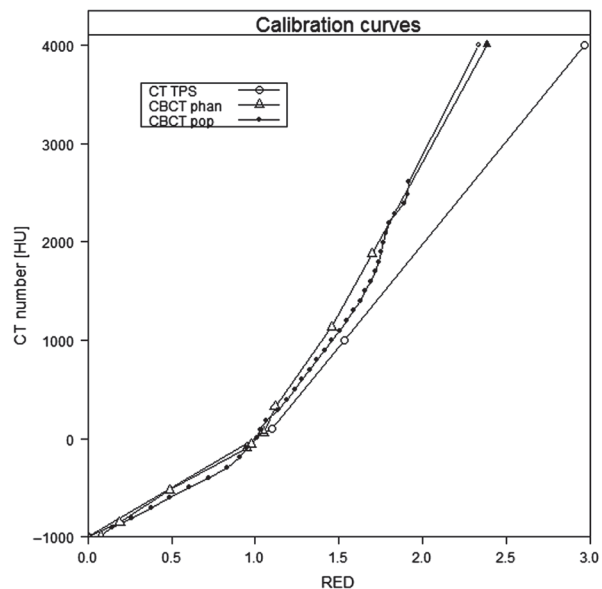


Figure 1. The different calibration curves converting CT numbers to electron densities relative to water (RED). Open circles: The default CT calibration curve in the treatment planning system (TPS). Triangles: The phantom based calibration curve (phan). Closed circles: The population-based calibration curve (pop). The population-based CBCT curve is for Patient 2 and produced from Patient 1 and 3–6. The CBCT curves are extrapolated using the 2 (phan) and 5 (pop) last data points. The extrapolated points are marked with a closed triangle (phan) and an open circle (pop), respectively.

the calibration curve with the corresponding CBCT bins. The final population-based CBCT calibration curve was an average of the five patients. Two patients' CBCT had slices with ring artifacts which were excluded for the population-based calibration and subsequent pCT error estimates.

pCT error estimates

The CT numbers and RED of the raw paired pCT-CT and pCT-CBCT data were averaged in bins of 10 HU and 0.01 RED across the entire tissue range, respectively (see Figure 2). The absolute difference, i.e. the absolute error, between the pCT-CBCT and pCT-CT data was calculated for each bin and the median value of the binned absolute errors found (MeAE). By looking at the binned errors, each bin over the tissue range will contribute equally to the error estimate independent of the number of data points within each bin. This estimate was chosen since most data points ($\approx 70\%$) are found within $\pm 10\%$ of water (RED = 1) where the error is usually small. Bins with less than 10 data points were excluded in the error estimate representing a maximum of 8% and 0.003% of the total number of bins and data points, respectively. A statistical pairwise TukeyHSD

analysis was carried out between the pCT-CT and pCT-CBCT binned absolute errors. The TukeyHSD decreases the risk of detecting a false positive result, i.e. significance, as compared to a t-test [14]. Significance was set to a p-value < 0.01 . Prior to the statistical analysis, the binned absolute error distributions were found to be independent and approximately normally distributed with constant variances. The TukeyHSD test was not applied to the transformation matrices since pairing of data is not possible for this test.

Results

The absolute match parameters for each patient were different as the initial position varied from patient to patient. The relative differences from the standard CT in the transformation matrices, however, were comparable and were investigated for significantly different shifts in each match direction. The differences in the CBCT match parameters when using MRI or pCT as reference instead of the standard CT scan showed that no significance from the CBCT-CT reference could be found (see Supplementary Table I, available online at: <http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1062546>).

On the basis of the calibration curves and absolute error calculations shown in Figures 1 and 2, respectively, Table I displays the MeAE of pCT with respect to the CT (reference) and CBCT. Without any correction, the error estimate using CBCT was about 100 HU higher than the CT-based error estimate and significantly different. The RED estimates were not significantly different using CBCT as compared to the reference CT when applying the population-based calibration.

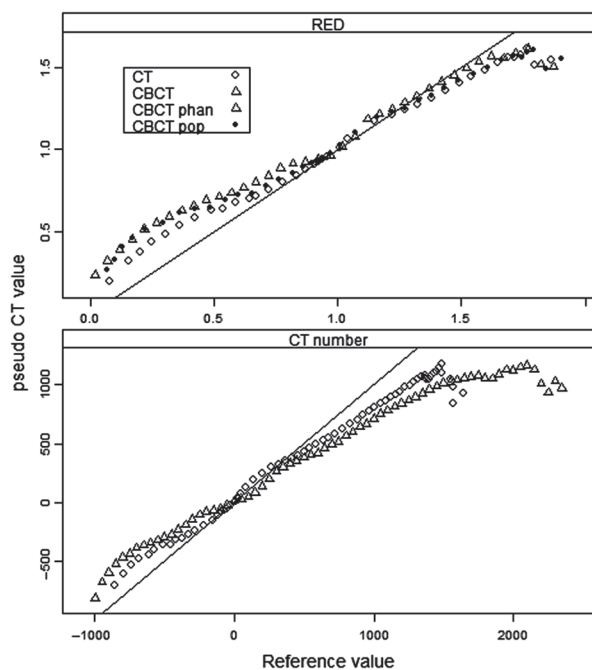


Figure 2. Paired data of pseudo CT versus the CT or CBCT data used for reference in the error estimates. The relative electron densities (RED, top) or the absolute CT numbers in HU (bottom) of the pseudo CT versus the CT (open diamond), CBCT phan (triangle, top), CBCT (triangle, bottom) and CBCT pop (closed circle). CBCT phan = RED assignment based on the CBCT phantom. CBCT pop = RED assignment based on the average of five patients (1–2, 4–6). The figure shows every fifth data bin used for the error estimates of Patient 3.

Discussion

MRI guidance is currently migrating into radiation oncology on many levels [9]. The main application of MRI is probably delineation but much effort is investigated into functional MRI as surrogates for prognostic and diagnostic purposes. Further studies investigating the benefits of performing online inter- and intrafractional MRI guidance are currently ongoing. Another branch of this active research area is MRI-only based RT [6–8,15]. Here, we investigated the possible benefits of combining an MRI-only based workflow with conventional x-ray based CBCT image guidance. We found good agreement between the CT-CBCT, MR-CBCT and pCT-CBCT match results with maximum deviations < 1 mm and 1° . Hence, we conclude that a satisfactory registration between a CBCT and an MRI or a pCT can be made without any systematic changes in the

Table I. Median absolute error (MeAE) estimates of the binned data (displayed for Patient 3 in Figure 2). Column 1: Patient number. Column 2: MeAE in HU for pCT-CT and pCT-CBCT with corresponding p-values. Column 3: MeAE in $\text{RED} \cdot 10^3$ for pCT-CT, pCT-CBCT_{phan} and pCT-CBCT_{pop} with corresponding p-values. The last row shows the average values and standard deviation of the MeAE for the six patients.

Patient	MeAE _{HU}			MeAE _{RED} · 10 ³				
	CT	CBCT	p-Value	CT	CBCT _{phan}	p-Value	CBCT _{pop}	p-Value
1	239	313	$< 10^{-15}$	153	98	> 0.5	131	> 0.14
2	159	278	$< 10^{-15}$	93	101	> 0.8	80	> 0.4
3	161	277	$< 10^{-15}$	87	124	0.001	97	> 0.01
4	215	303	$< 10^{-15}$	121	93	> 0.9	96	> 0.2
5	161	266	$< 10^{-15}$	93	101	0.001	95	> 0.01
6	168	359	$< 10^{-15}$	102	109	> 0.2	97	> 0.6
avg	184 ± 34	299 ± 34		108 ± 25	104 ± 11		99 ± 17	

transformation directions as compared to a standard CT-CBCT match. This is similar to or better than results previously reported for CT-CBCT versus MR-CBCT matches for the brain [10]. Also, the results are very similar to CBCT matches obtained in the pelvic with CT, MRI and pCT as the reference [11]. One could argue that part of the CT to MRI variation is removed when placing them into the same frame of reference before matching with CBCT (pCT is per default in the same reference as MRI from which it was predicted). It is difficult to see, however, how a CBCT match study could be constructed without introducing this step at some point.

CBCT-based error estimates of pCT were introduced to see whether CBCT could be used to verify the correctness of pCT and hence the geometric and corresponding dosimetric uncertainty associated with the treatment planning at the first fraction. If unacceptable errors based on CBCT are detected, the treatment can be stopped and the patient re-scanned with a conventional CT. A treatment based on this scan could then be applied for the remaining number of fractions. We have chosen to quantify the error estimate using a MeAE metric. The MeAE is probably a more fair measure of the true error of pCT as compared to the more widely reported mean absolute error (MAE) which is lowered by the many data points around water where the error in pCT is usually small. The corresponding average MAE for the six patients was 90 HU and 151 HU for the CT and CBCT, respectively. This difference is caused by the higher HU assignment of CBCT in the bone region (see Figure 2 bottom). The planning CT and CBCT were carried out at 120 and 100 kV, respectively, which is clinical routine and causes a difference in the HU estimates. Hence, it was expected that a difference between the CT and CBCT error estimates could be observed which is why the CT numbers were converted into relative electron densities. The CT-CBCT HU difference could probably

be reduced by carrying out the scans at equal energies. This is, however, currently not standard practice in our clinic. The scatter contribution has further been shown to be an important component to influence the CT number estimate of CBCT [16]. Transferring the data into relative electron densities (RED) brings the CT and CBCT MeAE value closer. For the phantom based calibration, Patients 3 and 5 showed a significant difference. These patients also displayed a low p-value for the population based CBCT calibration. From inspection of the boxplots, however, it is hard to identify what caused this low p-value as compared to the error boxplots in HU where the significance was more obvious (see e.g. Patient 5 in Supplementary Figure 2, available online at: <http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1062546>). From Figure 1, we found that it is challenging to simulate the exact scatter conditions of a brain geometry with a phantom. Instead, the scatter contribution was simulated using the true patient geometries which are very similar for the six patients. The population-based calibration curve is positioned somewhat in between the default CT and phantom-based calibration curves for electron densities above water. This trend is quite similar for all the investigated patients. Therefore, we do not expect the number of patients to have a large influence on the population-based CBCT calibration curve. The idea is then to obtain a population-based CBCT calibration curve for a given patient geometry prior to introducing MRI-only based treatment.

We conclude that CBCT can be used for patient setup of the brain with either MRI or pCT as the reference match modality. The correctness of pCT can further be verified from CBCT using a population-based calibration curve in the treatment geometry.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

- [1] Khoo VS, Adams EJ, Saran F, Bedford JL, Perks JR, Warrington AP, et al. A comparison of clinical target volumes determined by CT and MRI for the radiotherapy planning of base of skull meningiomas. *Int J Radiat Oncol Biol Phys* 2000;46:1309–17.
- [2] Rasch C, Steenbakkers R, van Herk M. Target definition in prostate, head, and neck. *Semin Radiat Oncol* 2005;15:136–45.
- [3] Ulin K, Urie MM, Cherlow JM. Results of a multi-institutional benchmark test for cranial CT/MR image registration. *Int J Radiat Oncol Biol Phys* 2010;77:1584–9.
- [4] Daisne JF, Sibomana M, Bol A, Cosnard G, Lonneux M, Gregoire V. Evaluation of a multimodality image (CT, MRI and PET) coregistration procedure on phantom and head and neck cancer patients: Accuracy, reproducibility and consistency. *Radiother Oncol* 2003;69:237–45.
- [5] Korsholm ME, Waring LW, Edmund JM. A criterion for the reliable use of MRI-only radiotherapy. *Radiat Oncol* 2014;9:16.
- [6] Johanson A, Garpebring A, Karlsson M, Asklund T, Nyholm T. Improved quality of computed tomography substitute derived from magnetic resonance (MR) data by incorporation of spatial information – potential application for MR-only radiotherapy and attenuation correction in positron emission tomography. *Acta Oncol* 2013;52:1369–73.
- [7] Edmund JM, Kjer HM, Van Leemput K, Hansen RH, Andersen JAL, Andreassen D. A voxel-based investigation for MRI-only radiotherapy of the brain using ultra short echo times. *Phys Med Biol* 2014;59:7501–19.
- [8] Andreassen D, Van Leemput K, Hansen RH, Andersen JA, Edmund JM. Patch-based generation of a pseudo CT from conventional MRI sequences for MRI-only radiotherapy of the brain. *Med Phys* 2015;42:1596–605.
- [9] Lagendijk JJ, Raaymakers BW, Van den Berg CA, Moerland MA, Philippens ME, van Vulpen M. MR guidance in radiotherapy. *Phys Med Biol* 2014;59:R349–69.
- [10] Buhl SK, Duun-Christensen AK, Kristensen BH, Behrens CF. Clinical evaluation of 3D/3D MRI-CBCT automatching on brain tumors for online patient setup verification – A step towards MRI-based treatment planning. *Acta Oncol* 2010;49:1085–91.
- [11] Korhonen J, Kapanen M, Sonke JJ, Wee L, Salli E, Keyrilainen J, et al. Feasibility of MRI-based reference images for image-guided radiotherapy of the pelvis with either cone-beam computed tomography or planar localization images. *Acta Oncol* 2015;54:889–95.
- [12] Eclipse Reference guide. Registration, smartadapt and contouring reference guide. Palo Alto, USA: Varian Medical Systems; 2013.
- [13] ICRU report 42. Use of computers in external beam radiotherapy procedures with high-energy photons and electrons. Bethesda, USA: ICRU; 1987.
- [14] Crawley MJ. The R book, 1st ed. Milton, Queensland: John Wiley & Sons; 2007.
- [15] Kapanen M, Tenhunen M. T1/T2*-weighted MRI provides clinically relevant pseudo-CT density data for the pelvic bones in MRI-only based radiotherapy treatment planning. *Acta Oncol* 2013;52:612–8.
- [16] Thing RS, Bernchou U, Mainegra-Hing E, Brink C. Patient-specific scatter correction in clinical cone beam computed tomography imaging made possible by the combination of Monte Carlo simulations and a ray tracing algorithm. *Acta Oncol* 2013;52:1477–83.

Supplementary material available online

Supplementary Figure 1–2 and Table I available online at: <http://informahealthcare.com/doi/abs/10.3109/0284186X.2015.1062546>